REMARKS

The following claims are currently amended:

(A) Pending claims: 1, 3, 4, 6, 9, 18, 23-28, 30-32 and 34;

(B) Withdrawn claims: 54, 55, 59-63, 65 and 72.

Claims 5 has been cancelled without prejudice or disclaimer, its subject matter having been basically incorporated into claim 1.

The unelected, withdrawn claims are being amended so that they remain commensurate in scope with the elected product claims for later rejoinder.

Applicants acknowledge and thank the Examiner for withdrawing the rejection under 35 U.S.C. §102(a) and the rejection of claim 17 under 35 U.S.C.§112, 2nd paragraph.

All the amendments are supported by the original claims and throughout the specification. No new matter is added by these amendments. Entry and allowance of the amended claims is respectfully requested.

I. NEW REJECTION UNDER 35 U.S.C. § 102(b)

The Office rejected the claims as anticipated under § 102(b) for the reasons detailed below. In light of Applicants amendment and remarks, it would be appropriate to withdraw this rejection.

A. Rejection under § 102(a)

Claims 1, 3, 4, 18, and 20-26 were rejected under 35 U.S.C. 102(b) as being anticipated by Caggana *et al.* (*J. Virol. 67*:4797-4803, 1993) ("Caggana"). According to the Office, Caggana teaches coxsackievirus CB4-P/CB4-V chimeras in which an attenuated virus strain, CB4-P, expresses "heterologous" proteins from CB4-V of various types at various regions of the CB4-P genome, including coding sequences "just downstream from codon 129 of VP1" (citing to page 4797-4798, "Construction of recombinant viruses"; page 4798, Fig. 1; and the paragraph bridging pages 4799 and 4801). The Office points to the definition of "heterologous" at page 12, lines 28-30, of the instant specification ("...refers to a polypeptide which is not otherwise naturally expressed by the virus"). The Office Action concludes that CB4-V proteins (including capsid protein), are heterologous with respect to the attenuated CB4-P, so that Caggana anticipates the enumerated claims.

B. Applicants' Response

Caggana is a publication by the present lead inventor and her colleagues. Dr. Ramsingh in her Rule 132 Declaration ("Ramsingh2 Declaration") has set forth several key distinction which highlight that Caggana does not anticipate the presently amended claims. The only "heterologous" polypeptides (to the CB4-P virus) disclosed in Caggana are those of a very closely related CB4-V strain, which show more than about 99.5% sequence identity (nucleotide and amino acid), when analyzed over several regions that co-inventor Ramsingh and her colleagues sequenced (Ramsingh, A *et al.* (1992) "Identification of candidate sequences that determine virulence in Coxsackievirus B4." *Virus Res. 23*:281-292). On that basis, it would be a "stretch" to consider these viruses "heterologous."

Notwithstanding the foregoing, Applicants respectfully direct the Examiner's attention to amended independent claims 1 and 18 (and all claims dependent therefrom). The claims now require that the heterologous DNA and heterologous polypeptides not originate from coxsackieviruses. There is ample support in the specification for such types of heterologous nucleic acids and polypeptides. The two families of exemplified heterologous polypeptides are (a) peptides of the protein ovalbumin (Example I, beginning at page 56, line 26) and (b) peptides of HIV gag p24 (Example II, beginning at page 65, line 17). Moreover the specification states that the invention can be used to induce immune responses against "...other pathogens ... such as retroviruses, lentiviruses, and immunodeficiency viruses, such as HIV, SIV, FIV and the like." (at page 18, lines 9-13). The long paragraph bridging pages 19 and 20 provides an extensive list of pathogens whose antigens could serve as the heterologous polypeptides encoded by the heterologous nucleic acids of the invention. In fact, the vast majority of heterologous nucleic acids and polypeptides considered to be of interest in the specification are "non-coxsackievirus" nucleic acids and polypeptides.

Additionally, the Caggana constructs involved replacement of CB4-P sequences with sequences of the same size from CB4-V (see Ramsingh2 Declaration, section 6). The present specification describes "insertion" cloning wherein heterologous DNA sequences such as those encoding ovalbumin or HIV gag p24 peptides are "inserted" into the CB4-P cloning vector and are expressed as fusion proteins with the viral capsid proteins. Claim 1 claims virions in which the heterologous polypeptides are fused to a viral capsid protein, reflecting such insertion cloning. There was no insertion cloning in Caggana.

Thus, Applicants believe that the foregoing provides ample evidence that Caggana does not anticipate any of the present claims. It would therefor be proper to withdraw this ground for rejection.

II. REJECTION UNDER 35 U.S.C. § 103(a)

The Office Action has maintained the previous rejection, now applied to claims 1, 3-6, 13-15, 17, 18, 20-23, and 28, which are allegedly obvious over Tracy *et al.*, WO 98/39426 (**"Tracy"**). For the reasons detailed below, Applicants respectfully submit that it would be appropriate to withdraw this rejection.

A. Specific Rejection

According to the Office Action, Tracy discloses

> [C]oxsackie virus B serotypes 1-6 and attenuated coxsackievirus vectors for delivery of nucleic acids encoding antigenic or therapeutic products, where heterologous nucleic acids may be inserted, for example between a coding sequence for a capsid protein and coding sequence of viral protease, or at the start of the genome's open reading frame or at other locations.

Importantly, as discussed below, Tracy describes results only with coxsackie virus B3 (CVB3). However, according to the Examiner, because Tracy discloses high level of organizational similarity among coxsackieviruses,

> any of the coxsackievirus B serotypes or other coxsackieviruses can be attenuated and modified for use as expression vectors for heterologous nucleic acids in the same manner as otherwise taught by Tracy *et al.*

emphasis added. This led the Office to conclude that it would have been obvious to make a recombinant attenuated CVB4 with an inserted heterologous nucleic acid "at the start of the genome's reading frame, *i.e.*, at the start of the sequence that encodes VP4." This conclusion by the Office relies on the notion that a "high level or organizational similarity" among the coxsackievirus serotypes would create an **expectation** that one could similarly genetically manipulate any CVB and obtain an equivalent expression vector.

B. Applicants' Response

Applicants' previous arguments focusing on aspects of virulence/pathogenicity of various CVB strains, *etc.*, were found not to be persuasive by the Office for several reasons.

Notwithstanding Applicants' belief that all the points they raised previously are accurate and cogent to their position that the claims are not obvious, they wish to direct the Examiner's attention to a number of other factors not previously highlighted that are important for appreciating the distinction of the present claims from Tracy. Again, the Ramsingh2 Declaration sets forth the relevant scientific background and facts in sections 8-11. The present amendments should moot the obvious rejection when the "limitations" of the Tracy disclosure and its divergence from the present invention are taken in to account. Thus, Applicants trust that the remarks below coupled with the Ramsingh2 Declaration will help the Office appreciate these differences and recognize the nonobviousness of the present claims.

The Office has taken the position that Tracy's disclosure of engineering a coxsackie B virus-3 by inserting a heterologous nucleic acid at the start of the genome's reading frame, *i.e.*, at the 5'UTR-P1 junction, is not patentably distinct from the present claims. This view is in need of rectification. As noted in the Declaration at section 11, any polypeptide expressed from a nucleic acid inserted at this location (or at Tracy's truly preferred and exemplified location, the P1/P2 junction) will never be expressed as part of the virion structure. Thus, the foreign protein could not possibly be fused to a viral capsid protein in the virion, as required in the independent claims (1 and 18). A ***virion*** produced according to Tracy would only be "recombinant" with respect to its RNA genome, as there would be no recombinant proteins (comprising a heterologous sequence) anywhere in or on such a virion.

Indeed a heterologous polypeptide per Tracy can only be expressed during transcription and translation of the infecting genome, and then, it would be removed from any viral proteins. That appears to be Tracy's goal, as the only exemplified heterologous protein expressed in the cited publication was murine IL-4 (which was clearly not intended to serve as an "antigen" to induce an anti-IL-4 immune response). Given Tracy's goal, it would not have been logical to express IL-4 in any other way, *a fortiori* in a form fused to a viral capsid protein that would be part of the virion's structure as recited in the present claims. It is rather doubtful that IL-4 would maintain its biological function in such a context The heterologous polypeptide engineered according to the Tracy disclosure would be removed from the viral polyprotein during processing. This is in stark distinction from the present invention, where the heterologous polypeptide is not removed, but rather is integrated into the sequence of a viral capsid protein (and, as recited in various dependent claims, is part of VP1, is in an immunogenic region of VP1, and is part of, a T or B cell epitope of VP1.

To reiterate, the virions and nucleic acids claimed herein require that the encoded heterologous polypeptide be a physical part of the virion, totally ruling out the option of inserting the nucleic acid where Tracy discloses to do so. As such a capsid fusion present in the virion's coat, , the heterologous polypeptide is endowed with the desirable property of immunogenicity so that it can stimulate various T cells and B cells (and ultimately generate a protective immune response against any molecule, cell or organism from which the epitope(s) is(are) derived.. In contrast, as noted in the Ramsingh2 Declaration, if a heterologous polypeptide were expressed according to the Tracy method, and if it further had the requisite structure to be recognized by a host immune system, it could only (if at all) serve as a CTL epitope.

In view of the facts set forth in the Ramsingh2 Declaration and the remarks above, it should be clear that Tracy does not in any way suggest or motivate the presently claimed invention, much less provide any expectation of success. If anything, it could be said that Tracy teaches away from this invention; following Tracy's teaching would **not** lead one to the present claims. Hence, the present claims cannot be considered obvious over Tracy. The Examiner is therefore requested to withdraw the pending §103(a) rejection.

For the record, Applicants wish to respond to several additional statements in the Office Action that relate to the Office's analysis of their earlier arguments. In considering Applicants' "point (2)" in support of nonobviousness, the Office Action stated that:

> "the features upon which applicant relies (*i.e.*, that the vector not be a pathogen in the species in which it is being used) are not recited in the rejected claim "

This is not accurate. Claim 1, both now and in its earlier iteration was directed to an "attenuated coxsackievirus B4 virion." It is fairly accepted in the art that "attenuated" means "nonpathogenic." Thus, the claim did indeed include the limitation being argued. In the legal analysis immediately thereafter that was directed to the notion of reading limitations from the specification into the claims, the Office Action stated that "even if a such a limitation were recited, it would likely represent intended use only and not necessarily be entitled to be given patentable weight." Applicants do not believe this analysis applies here given the specifics of the claim under consideration and the nature the invention as a whole. Obviously, the adjective "attenuated" is not as "precise" a physical property as weight, shape or color. Does a virus "have" the property of being attenuated (a) when it sits in a tube in a freezer, or (b) only after it is inoculated into a potentially sensitive subject and

cannot produce a pathogenic effect? Semantically, it may be that "attenuated" doesn't apply in (a). However, in the real world of virology, it would be considered by those skilled in the art to be a fundamental trait of a virus, just as "globular" is a trait of a globular protein (at least when the protein is maintained under certain conditions). Applicants believe that if one were to follow the term "attenuated" in a claim with words like "when it is administered to a host," one would not be adding to or further clarifying the meaning of "attenuated" as that word is understood in the art. Therefore, it is Applicants' position that "attenuated" as used in the present claims does carry patentable weight.

III. COMMENTS ON OTHER AMENDMENTS

A.. Amendments of Withdrawn Claims

In anticipation of rejoinder of method claims of appropriate scope, Applicants have amended various of claims 54-72, in part to maintain their scope in consonance with the claims being examined. In addition, Applicants have removed the language reciting a separate "providing" step in claims 54, 55, 59-63, 65 and 72, as such language is extraneous. The composition being administered in what was formerly "step (b)" is now incorporated into a single clause that defines what is being administered in these method claims.

B. Improvement in Clarity and Precision

A number of the current amendments were voluntary, and not introduced in response to any objections or rejections by the Office. Rather, it was noticed that the language in some claims was not as precise or artful as it could be, so it is now being amended. Several examples follow:

In claims 1, 6 and 10, the term "expressed" was used to describe the form or location of the heterologous protein. Because "expression" has taken on an meaning in molecular biology that relates to transcription and translation of a gene into a gene product (protein), Applicants found a more precise way to describe the claimed subject matter. Thus, in claim 1, the heterologous polypeptide which is "expressed by the virion" is now recited as "fused to a capsid protein of the virion." Similarly, in claim 6 and 10, instead of the heterologous polypeptide being "expressed" within an immunogenic region, the amended claim now states that the polypeptide is "situated" within an immunogenic region.

Rather than stating that the heterologous nucleic acid is "in" the P1 region, amended claim states that the nucleic acid is "inserted" in the P1 region.

Applicants have moved away from using the word "contain" when referring to regions and sequences of molecules. For example, in claim 9, the immunogenic region of VP1 no longer "contains B cell epitopes..." but rather "comprises" the epitopes.

In claims 18 *et seq.*, Applicants have adopted a more abbreviated form of language. The heterologous nucleic acid is described as an "insert", so that all subsequent references back to this term read "the insert" rather than "the heterologous nucleic acid."

In several of the "withdrawn" claims, the antecedent basis was not as precise as it could have been. Thus, claim 59, dependent from claim 32, previously read: "...**the recombinant attenuated CB4-P virion of claim 32...**". However, claim 32 was directed to a nucleic acid with certain properties (that constitutes the genome of the CB4-P virion of the earlier claim). Therefore it was deemed more precise in terms of antecedent basis to recite "**a recombinant attenuated CB4-P virion comprising the nucleic acid of claim 32**". This was introduced into amended claim 59 and several other similar claims.

None of these amendments is believed to introduce new matter or to fun afoul of any of the statutory requirements under 35 U.S.C. § 112. It is therefore requested that these amendments be entered and considered.

IV. CONCLUSION

In conclusion, it is respectfully requested that the above amendments, remarks and requests be considered and entered. Applicant respectfully submits that all the present claims are free of the prior art of record, and are therefore in condition for allowance. Applicants respectfully request early notice of such favorable action.

Examiner Wortman is respectfully requested to contact the undersigned at (202) 344-8584 with any questions or comments if they will assist in the understanding this amendment and response. Furthermore, since there have been no interviews in this case, the undersigned requests the opportunity of an interview with the Examiner if there are continuing questions of patentability of these claims.

Applicants also note that references cited in the Ramsingh2 Declaration and in the present document are not being provided at this time as they are not believed to be necessary to the understanding of the points for which they are cited. If the Examiner has a different view, Applicants will be happy to provide them.

In the unlikely event that the Patent and Trademark Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due to **Deposit Account 22-0261**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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